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| EXAMINER | |
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| WELTER, RACHAEL E | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/517,157 | BREITENBACH, ARMIN | |
| | Examiner | Art Unit | |
| | RACHAEL E. WELTER | 1611 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *08 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *12-28* is/are pending in the application.

4a) Of the above claim(s) *20-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 December 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Claim Status*

Claims 12-28 are pending. Claims 12-19 are directed to the elected species. Claims 19-28 are withdrawn. Claims 1-11 are cancelled.

### *Acknowledgements*

Receipt of the amendment and remarks/arguments filed on December 8, 2008 is acknowledged.

### *Claim Objections*

The objections of claims 12 and 19 are withdrawn in light of applicant's amendment.

### *Drawings*

The drawings are objected to because they are of poor quality and unclear, especially figures 1 and 2. Figures 1 and 2 appear to be microscopic images, in which its features are barely recognizable. Figures 3-6 are not clear as a result of poor photocopying. Appropriate correction is required. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the

appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

**Claims 12-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lauterback et al (US Publication No. 2003/0027793) in view of Farinas et al (US Patent No. 5,906,830) and Taylor et al (WO 92/014442).**

Claims 12-19 are drawn a matrix for transdermal administering of rotigotine comprising a matrix polymer supersaturated with rotigotine base, wherein a portion of the rotigotine is dispersed in the matrix polymer as amorphous particles with a maximum mean diameter of 30 um. The matrix is free of solvents, crystallization inhibitors, and dispersants and could optionally include one or more antioxidants. The matrix polymer is an amine-resistant silicone or a mixture of amine-resistant silicones and is a self-adhesive. The contents of the matrix consist of 60-95 wt.% amine-resistant silicone, 5-40 wt.% amorphous rotigotine base, and 0-2 wt.% antioxidant. Furthermore, the system for transdermal administering of rotigotine comprises a backing that is impermeable to rotigotine. Finally, the rotigotine charge is between 0.3 - 6 mg/cm$^2$.

Lauterback et al teach a silicone-based transdermal therapeutic system that contains 0.1-3.15 mg/cm$^2$ of rotigotine as an active ingredient (abstract). According to Lauterback et al, the silicone-based system must contain at least one amine resistant silicone compound as the main component (paragraph 0017). Lauterback et al teach that usually the silicone compound will be a pressure sensitive adhesive and will form a matrix in which the other components of the system are embedded (paragraph 0017). Furthermore, Lauterback et al teach the amounts of composition components in a table found in paragraph 0041. Rotigotine base is 9 wt.%, the amine resistant silicone compound is 89 wt.%. Moreover, Lauterback et al teach the addition of antioxidants

such as ascorbyl palmitate, DL-alpha tocopherol, and sodium metabisulfate (table in paragraph 0041). These antioxidants are present at 0.02 wt.%, 0.05 wt.%, and 0.0006 wt.% respectively. Lauterback et al do not teach a transdermal system comprising a matrix polymer supersaturated with rotigotine base. In addition, Lauterback do not teach a matrix free of solvents, crystallization inhibitors, and dispersants. The use of a solubilizer is taught in paragraph 0022. Finally, Lauterback et al do not teach a backing layer for the transdermal system.

Farinas et al teach methods for manufacturing transdermal drug delivery systems containing supersaturated drug reservoirs (abstract). According to Farinas et al, a backing layer serves as the upper surface of the device and is substantially impermeable to the drug (column 4, lines 6-9). In addition, Farinas et al teach a polymer-drug admixture that results in a system with two liquid phases, one that contains polymer and one that contains drug (column 6, lines 36-41). Farinas et al teach that the drug phase when quenched rapidly becomes an amorphous, glass phase at ambient conditions (column 6, lines 42-44). Furthermore, Farinas et al teach that if a solvent is used, it is removed during or before heat treatment (column 8, lines 7-9). Farinas et al do not teach the addition of any crystallization inhibitors or dispersants and list that they are optional (column 8, lines 14-21). Finally, Farinas et al teach that the drug formulation may also include standard carriers or vehicles useful for facilitating drug delivery, like antioxidants (column 8, lines 14-16).

Taylor et al teach a composition for transdermal administration of a biologically active agent wherein the active agent is present in an amount above its solubility limit

and wherein the active agent is present in fine particles throughout said carrier to facilitate transdermal transfer of the composition (abstract). According to Taylor et al, at least 60% of the particles are sized at less than 20 microns (pg. 5, lines 3-4). Taylor et al teach that the rate of transdermal delivery of the active ingredient is increased and controlled by having at least a substantial proportion of the active compounds present in the form of fine particles (pg. 4, lines 9-15).

Therefore, it would have been obvious to an artisan of ordinary skill at the time the invention was made to make a transdermal system that contains a backing layer and supersaturated drug reservoirs free of solvents, crystallization inhibitors, and dispersants. One would have been motivated to use a backing layer to protect the upper surface of the device and prevent the drug from leaking out. Furthermore, one would have been motivated to use a matrix free of solvents, crystallization inhibitors, and dispersants to reduce costs, time and effort.

Therefore, it would have been obvious to an artisan of ordinary skill at the time the invention was made to make a transdermal system containing supersaturated drug reservoirs. One would have been motivated to make such a system because higher drug fluxes are obtained. In addition, one would have been motivated to make a system with an active ingredient present in the carrier in the form of fine particles to increase and control drug release.

***Response to Arguments***

Applicant's arguments filed 12/8/08 have been fully considered but they are not persuasive.

Applicant argues Lauterback does not constitute statutory prior art under 102 (b) and reserve the right to make a showing of earlier invention to disqualify Lauterback. However, applicant does not believe a showing of earlier invention is necessary. Applicant argues that with respect to claims 12 and 13 that it could not have been predicted by one of skill in the art at the time the invention was made that a storage-stable matrix could be prepared containing rotigotine base above its limit of solubility in the matrix polymer without solvents, crystallization inhibitors, or dispersants or any other excipient ingredient. Applicant argues that no reasonable expectation of success existed at the time of the present invention. In arguing the Lauterback reference, applicant admits that "supersaturated rotigotine base," which was amended to "...rotigotine base in a concentration above the solubility limit of rotigotine base in the matrix polymer" is not a point of distinction between the instant claims and Lauterback. Rather, applicant believes that the present invention is free of solvents, crystallization inhibitors, and dispersants, which Lauterback and WO 99/49852 do not teach. Applicant argues that Lauterback and WO '852 teach that rotigotine is only freely soluble in silicone and that the adding of additives to improve the solution characteristics of rotigotine is recommended, such as PVP taught in Lauterback. Applicant argues that the art of record emphasizes the importance of using a solubility-enhancing ingredient, such as PVP in providing a silicone polymer/rotigotine base matrix providing acceptable skin flux of rotigotine. Applicant further argues that Farinas

exemplifies an unrelated compound, namely estradiol, as the active agent in a transdermal composition. Furthermore, applicant submits that an artisan of ordinary skill reading Farinas' disclosure of "optional" inclusion of crystallization inhibitors in combination with Lauterback would be lead to believe that a crystallization inhibitor is not necessary for rotigotine. Applicant believes no rationale has been suggested for one skilled in the art to have gone against the teach of Lauterback and WO '852 to attempt to prepare a matrix comprising a matrix and rotigotine base without solvents, crystallization inhibitors, or dispersants.

In response to applicant's arguments, applicant has made no showing of earlier invention to disqualify Lauterback. Thus, the rejection is still pertinent and the rejection is maintained. In response to the arguments against Lauterback, the examiner admitted in the previous action that the TDS comprising rotigotine of Lauterback does not teach a matrix free of solvents, crystallization inhibitors, and dispersants. Because Lauterback lacks this teaching, the examiner combined Lauterback with Farinas. When comparing the method of preparing the matrix in the instant specification with Farinas, the examiner notes that there are similarities. The instant invention does not use any solvents, crystallization inhibitors, or dispersants because crystalline rotigotine is converted into the amorphous form by heating the matrix to a temperature above the melting point of rotigotine. Like the instant invention, Farinas teaches heating an admixture of polymer and rotigotine to a temperature that is higher than the actual melting temperature of the pure drug contained in the formulation to provide a system containing two liquid phases, one liquid phase comprising polymer and one liquid phase

comprising drug formulation (column 3, lines 56-67). Furthermore, Farinas teaches that when the phase containing drug is quenched rapidly, it results in an amorphous, glassy phase at ambient conditions (column 6, lines 42-44). Farinas teaches that this method is particularly useful for drug-polymer systems wherein the drug has relatively low solubility in the polymeric material, which is preferably silicone adhesives (column 6, lines 51-60). Farinas also teaches that drugs which may be incorporated into the transdermal system include dopaminergic agonists. As evidenced by Lauterback, rotigotine base is a dopamine receptor agonist (paragraph 0001). According to Farinas, a solvent may be used but it is removed during or before heat treatment and the drug formulation may include crystallization inhibitors or other standard carriers or vehicles useful for facilitating drug delivery (column 8, lines 14-21). Farinas teaches these supersaturated transdermal drug delivery systems enable higher drug fluxes to be obtained.

Therefore, the examiner believes it would have been obvious to an artisan of ordinary skill at the time the invention was made to modify the transdermal delivery system comprising rotigotine base of Lauterback into the transdermal delivery system disclosed in Farinas. Because Farinas teaches that dopaminergic agonists can be used as active agents in its supersaturated drug reservoirs, one would have predicted with a reasonable expectation of success that the rotigotine transdermal delivery system of Lauterbach could be modified to include characteristics of Farinas, including its elimination of solvents, crystallization inhibitors and dispersants. One would have been motivated to do so in order to obtain higher drug fluxes, as suggested in Farinas. Thus,

the examiner believes that there is enough rationale to modify the teachings of Lauterback and prepare a matrix comprising a matrix polymer and rotigotine base above the solubility therein without solvents, crystallization inhibitors, or dispersants as described in Farinas. Although applicant argues that Farinas teaches an unrelated compound, namely estradiol, Farinas also teaches dopaminergic agonists. The examiner reminds applicant that just because using dopaminergic agonists as a drug is not a preferred embodiment of the invention, it does not constitute a teaching away. According to MPEP 2123, disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. *In re Susi, 440 F.2d 442, 169 USPQ 423 (CCPA 1971).* In addition, it should be noted that the process of preparing the matrix of Farinas is similar and includes heating the drug and polymer to a temperature above the melting point of the drug. Furthermore, the examiner disagrees with applicant that the optional inclusion of crystallization inhibitors in Farinas would not lead an artisan to eliminate crystallization inhibitors in the transdermal delivery system of Lauterback. According to MPEP 2144, omission of an element and its function is obvious if the function of the element is not desired. *Ex parte Wu, 10 USPQ 2031 (Bd. Pat. App. & Inter. 1989).* Since Farinas teaches that crystallization inhibitors may be incorporated, Farinas clearly suggests a transdermal drug delivery system free of crystallization inhibitors.

Applicant further argues that Taylor is cited for discussing an active agent present in fine particles. Applicant argues that the present claims are specific in reciting amorphous particles. However, applicant points out that Taylor teaches particles that

are crystals not amorphous particles. Applicant does not believe Taylor as a whole provides motivation for one of skill in the art to prepare a matrix containing amorphous rotigotine particles. Finally, applicant argues that one of ordinary skill in the art would not have predicted that after 12 months storage, no signs of rotigotine crystallization or change in particle size would be observed. Applicant submits that no prima facie case of obviousness has been established with respect to claims 12-13 and its dependent claims.

In response to applicant's arguments, the examiner argues that Taylor was solely cited to disclose the particle size in the instant claims and to establish the state of the prior art. Taylor is only used as evidence to establish that particles sizes having a maximum mean diameter of 30 um can be obtained in a transdermal delivery system. Even though Taylor teaches crystal particles, Farinas teaches that when a phase containing drug is quenched rapidly, it results in an amorphous, glassy phase at ambient conditions. Therefore, it would have been obvious from the teachings of Farinas that amorphous particle would have been obtained. In fact, Figure 2 of Farinas discloses what looks like particles of drug (12a). Furthermore, Taylor provides motivation of why one would want particles of drug resulting from the active agent being in a carrier at a level above its solubility. Taylor teaches that the rate of transdermal delivery of the active ingredient is increased and controlled by having at least a substantial proportion of the active compounds present in the form of fine particles (pg. 4, lines 9-15). Therefore, the examiner reiterates that Taylor is only incorporated for

the teaching of its particle sizes regardless if they are crystal particles. Farinas suggests the obvious incorporation of amorphous particles.

Therefore, the examiner believes it would have been obvious to an artisan of ordinary skill at the time the invention was made to modify the transdermal delivery system of Lauterback and incorporate characteristics of the transdermal delivery system of Farinas (elimination of solvent, crystallization inhibitors, dispersants) with the particles sizes disclosed in Taylor. One would have been motivated to do so in order to obtain higher drug fluxes and a controlled drug release rate, as suggested by Farinas and Taylor respectively. Regarding applicant's argument that an artisan of ordinary skill would not have predicted that after 12 months storage, no signs of crystallization or change in particle size would be observed, the examiner believes that proper rationale is given as stated above for combining the references. Therefore, the result of obtaining no signs of crystallization or change in particle size after 12 months storage would be an expected result of the obvious transdermal delivery system of Lauterback, Farinas, and Taylor.

***Conclusion***

Claims 12-19 are rejected. No claims are allowed.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to RACHAEL E. WELTER whose telephone number is (571) 270-5237. The examiner can normally be reached 7:30-5:00 Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau can be reached at 571-272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

REW

/Lakshmi S Channavajjala/
Primary Examiner, Art Unit 1611
February 27, 2009